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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/773,042	01/31/2001	Ronald M. Evans	033123-002	1752

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EXAMINER	
PAK, MICHAEL D	

ART UNIT	PAPER NUMBER
1646	

DATE MAILED: 03/25/2004

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/773,042	EVANS ET AL.	
	Examiner	Art Unit	
	Michael Pak	1646	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☐ Responsive to communication(s) filed on _____.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1,2,4,5 and 7-15* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1,2,4,5,7-15* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. §§ 119 and 120

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

13)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application) since a specific reference was included in the first sentence of the specification or in an Application Data Sheet. 37 CFR 1.78.

a) ☐ The translation of the foreign language provisional application has been received.

14)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121 since a specific reference was included in the first sentence of the specification or in an Application Data Sheet. 37 CFR 1.78.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449) Paper No(s) _____.
4) ☐ Interview Summary (PTO-413) Paper No(s). _____.
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other:

DETAILED ACTION

Reissue Applications

1. The original patent, or a statement as to loss or inaccessibility of the original patent, must be received before this reissue application can be allowed. See 37 CFR 1.178.

2. Applicant is notified that any subsequent amendment to the specification and/or claims must comply with 37 CFR 1.173(b).

3. Claims 1-2, 4, 5 and 7-15 are pending. Claims 3 and 6 have been cancelled.

Specification

4. The disclosure is objected to because of the following informalities. Column 9, lines 25-30 contains an old address of ATCC. It is suggested that an updated address of ATCC be used.

Appropriate correction is required.

5. The references cited in the reissue patents will not be printed automatically. It is suggested that references be cited in the form 1449 as a submission for information disclosure statement if applicant desires the publication of the references and patents relevant to the reissue patent.

Claim Objections

6. Claim 10 is objected to because of the following informalities. Claim 10 recite "phRAR1" while the specification on column 9, line 54 refers to the ATCC deposit 40392 as "phRARa". There appears to be inconsistency in the name. Appropriate correction is required.

7. Claims 9 and 11-14 are objected to because of the following informalities. Claims recite "claimed in any one of claims 10 or 1, 2, 4, 5, and 7" which is confusing because the alternative language of the dependent claims are not clear. Appropriate correction is required.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

8. Claims 1, 2, 4, 5, 7-9, and 11-15 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claims 1 and 4 recite the term "structurally and functionally related to steroid and thyroid hormone receptors" whose metes and bounds are not clear because it is not clear how the structures and functions are related. It is not clear how similar the structure or function has to be to define the metes and bounds of the term. It is not clear what way does the protein have to be similar in order to be related. Claims 2, 5, 9 and 11-15 are dependent on claims 1 and 4 and/or encompass the term.

Claim 4 recite the term "hormone binding and transcription-activating properties characteristic of retinoic acid receptor" whose metes and bounds are not clear because it is not clear what properties are characteristic of RAR versus just a property. Claims 1, 2, 5, 9 and 11-15 are dependent on claim 1 and/or encompass the term.

Claim 7 recites the term "DNA sequences" which is confusing because the multiple panels of the figures appear to break up the sequences thus creating a confusion when there is only one contiguous DNA sequence in Figure 1B1-3. It is suggested that the claim language reflect the single contiguous DNA sequence. An option to achieve this is to be in sequence compliance and claim the SEQ ID NO:. Furthermore, "DNA sequence" is not a product but a property of the product and it is suggested that the term "DNA" be used in the claim consistent with the other claims.

Claim 8 recite acronyms of chimeric receptors whose terms are not clearly defined and the metes and bounds of which are not clear. Examiner suggests that the full name of the acronym as supported by the specification be used in conjunction with the acronym which provides function and structure to the limitations.

9. Claims 1, 2, 4, 5, 8, 9, and 11-15 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. Written description rejection.

Claims 1, 2, 4, 5, and 8 are drawn to a genus of DNAs which encode a genus of retinoic acid receptors that are not defined by any critical or definitive structural limitations. Claims 9 and 11-15 are drawn to an even more broader genus encompassing DNAs which hybridize to the aforementioned genus of DNAs and encode proteins defined by function alone without any critical or definitive structural limitations. because of no structural limitation and the recitation of "hybridization" language. The specification only discloses a single species disclosed in Figure 1. The specification does not disclose what structural features, other than the full length sequence of the single species of figure 1, must be retained in order to render a protein as a retinoic acid receptor. The specification fail to disclose what specific functions are considered to be definitive of retinoic acid receptor and what specific structures are critical to their retention. The claims are drawn to a genus that need only be related or retain a function that is "characteristic" of a retinoic acid receptor without a definition of what functions are characteristic and what structures other than the full length sequence of figure 1 are required for said functions. Without said information, the single species cannot be representative of such a broad genus. *University of California v. Eli Lilly and Co. (CAFC) 43 USPQ2d 1398* (*Eli Lilly*) held that a generic claim to human, mammalian

or vertebrate protein when only the rat protein sequence was disclosed, did not have written description in the specification. The essential feature of the invention is the single species of DNA encoding the retinoic acid receptor of Figure 1. The specification with a single species does not provide support for the claimed genus because *Eli Lilly* held that one skilled in the art could not envision the structure of the genus of proteins in other species such as human or the genus of mammalian or vertebrate proteins. In the same manner, one skilled in the art cannot envision the genus of retinoic acid receptors structure and thus the specification does not provide adequate disclosure for the claimed genus.

10. Claims 1, 2, 4, 5, 8, 9, and 11-15 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for the substantially pure DNA of claim 7 and the isolated plasmid of claim 10, does not reasonably provide enablement for the substantially pure DNA of claims 1, 2, 4, 5, 8, and 9, the cells and methods of claims 11-15. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the invention commensurate in scope with these claims. The first paragraph of § 112 requires that the patent specification enable "those skilled in the art how to make and use the full scope of the claimed invention without `undue experimentation.'" Genentech, Inc. v. Novo Nordisk AIS, 108 F.3d 1361, 1365, 42 USPQ2d 1001, 1004 (Fed. Cir. 1997) (quoting In re Wright, 999 F.2d 1557, 1561, 27 USPQ2d 1510, 1513 (Fed. Cir. 1993)); see also In re Fisher, 427 F.2d 833, 839, 166 USPQ 18, 24 (CCPA

1970). ("[T]he scope of the claims must bear a reasonable correlation to the scope of enablement provided by the specification to persons of ordinary skill in the art."). Whether making and using the invention would have required undue experimentation, and thus whether the disclosure is enabling is a legal conclusion based upon several underlying factual inquiries. See In re Wands, 858 F.2d 731, 735, 736-37, 8 USPQ2d 1400, 1402, 1404 (Fed. Cir. 1988). As set forth in Wands, the factors to be considered in determining whether a claimed invention is enabled throughout its scope without undue experimentation include the quantity of experimentation necessary, the amount of direction or guidance presented, the presence or absence of working examples, the nature of the invention, the state of the prior art, the relative skill of those in the art, the predictability or unpredictability of the art, and the breadth of the claims.

Likewise, in Amgen Inc. v. Chugai Pharm. Co., 927 F.2d 1200, 18 USPQ2d 1016 (Fed. Cir. 1991), the court affirmed the holding of invalidity of claims to analogs of the EPO gene under § 112 for lack of enablement where applicants had claimed every possible analog of the EPO gene but had disclosed only how to make EPO and a very few analogs. "[D]espite extensive statements in the specification concerning all analogs of the EPO gene that can be made, there is little enabling disclosure of the particular analogs and how to make them .... There may be many other genetic sequences that code for EPO-type products. Amgen has told how to make and use only a few of them and is therefore not entitled to claim all of them." Id., 927 F.2d at 1213-14, 18 USPQ2d at 1027. Claims 1, 2, 4, 5, 8, 9 and 11-15 are too broad to be enabled by a specification that provides only one example of an embodiment of the claimed invention.

Here, independent claims 1, 4 and 8 are not limited to DNA encoding any specific retinoic acid receptor (i.e., RAR or RXR) of any specific isotype (e.g., RARα, RARβ or RARy) or isoform (e.g., RARα1 or RARα2) from any particular species (e.g., mammal, amphibian, bird or fish). Claim 4 is even broader than claim 1 insofar as it is directed to a DNA encoding a protein which has hormone-binding or transcription-activating properties characteristic of retinoic acid receptor." While dependent claims 2 and 5 are limited to DNA encoding a human retinoic acid receptor, they are also not limited to any specific retinoic acid receptor, isotype or isoform. The specification only describes one DNA sequence (i.e., phRARoc1) encoding one isoform of one isotype of one protein member of a "gene family" from only one species, i.e., human RARa1.

The amount of direction provided in the specification is limited to isolation and characterization of phRARa1. The specification has identified a range of nucleotides and amino acid which span the DBD and the LBD in hRARa and phRARoc1, but not which nucleotides and amino acids are critical to binding a retinoic acid ligand and a retinoic acid response element. Neither does the specification identify which amino acid and/or nucleic acid subsequences are conserved between either isotypes, e.g., RARα, RARβ or RARY, or between species, e.g., mammals, fish, amphibians or birds. Thus, the specification provides no evidentiary basis for reasonably predicting how the primary sequence homology correlates to structural/functional homology, The specification does not teach the critical amino acid/nucleic acid sequences necessary to bind retinoic acid and thereby unmasking the DBD of the receptor have not been identified. Even

proteins with highly homologous sequences can function very differently for example 3-hemoglobin and its gene in normal individuals and patients with sickle cell anemia.

Furthermore, to the extent that the Southern blot/low stringency hybridization analysis described in the specification might suggest the existence of one or more genes encoding other proteins with closely related properties to hRARα, The specification does not describe the isolation and characterization of these genes or how to make them. Moreover, the fact that other RAR's have been isolated, sequenced and characterized in subsequent publications does not lead to the conclusion that the specification taught how to make them. 24 Gould v. Quiaa, 822 F.2d 1074, 1078, 3 USPQ2d 1302, 1305 (Fed. Cir. 1987) ("A later dated publication cannot supplement an insufficient disclosure in a prior dated application to render it enabling.") Even the specification describes the hap gene identified by Dejean in 1986 and later identified as being the RAR gene, as giving an "unrelated" pattern under high stringency hybridization analysis.

Assuming arguendo that other DNA sequences were isolated by a low stringency hybridization analysis as described in the specification, whether those DNAs actually encoded retinoic acid receptors or encoded receptors for other ligands appears unpredictable, i.e., a ligand screening assay based on chimeric receptor constructs would have to be performed which would require undue experimentation. As to the state of the art, the modular nature or "domain" organization of nuclear receptor proteins "was first noted in a sequence alignment of the estrogen receptors of different species" by Krust et al. p. 1181, c. 1. Green's paper describes replacing the DBD of an estrogen

receptor protein with the DBD of a glucocorticoid receptor to produce a chimeric receptor, p. 851. Green stated that

> [o]ne important consequence of the results reported here is the possibility of creating chimaeras between trans-acting transcriptional regulatory factors that contain sequences homologous to the steroid hormone receptor region C [i.e., DBD] (c. 1, 13).

Thus, the state of the art appears to be evolving, rather than mature.

Therefore, based on the above Wands analysis, a preponderance of the evidence supports a conclusion that one skilled in the art would not have been enabled to make and use the invention of claims 1, 2, 4, 5, 8, 9 and 11-15 without undue experimentation.

11. Claim 10 is rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

The enablement of claim 10 requires the availability of ATCC Deposit No. 40392. This determination has been made because the claimed ATCC Deposit No. properties have not been fully disclosed or the materials required to construct the claimed ATCC Deposits have not been shown to be publicly known and fully available. The specification does not provide assurances that the deposited material will be made irrevocably available with no restrictions upon the issuance of the patent. Accordingly, it

is deemed that a deposit and ATCC Deposit No. 40392 should have been made in accordance with MPEP 2402.

If a deposit has been made under the terms of the Budapest Treaty, then an affidavit or declaration by Applicants or someone associated with the patent owner who is in a position to make such assurances, or a statement by an attorney of record over his or her signature, stating (a) that the deposit has been made under the terms of the Budapest Treaty; and (b) that all restrictions imposed by the depositor on the availability to the public of the deposited material will be irrevocably removed upon the granting of a patent, would satisfy the deposit requirements. See 37 C.F.R. ' 1.808. If a deposit is not made under the terms of the Budapest Treaty, then the requirements may be satisfied by an affidavit or declaration by Applicants or someone associated with the patent owner who is in a position to make such assurances, or by a statement by an attorney of record over his or her signature, stating that the deposit has been made at an acceptable depository and establishing that the following criteria have been met: (a) during the pendency of the application, access to the deposit will be afforded to one determined by the Commissioner to be entitled thereto; (b) all restrictions imposed by the depositor on the availability to the public of the deposited material will be irrevocably removed upon the granting of a patent; (c) the deposit will be maintained for a term of at least thirty (30) years and at least five (5) years after the most recent request for the furnishing of a sample of the deposited material; (d) a viability statement in accordance with the provisions of 37 C.F.R. ' 1.807 is provided; and (e) the deposit will be replaced should it become necessary due to inviability, contamination, or loss of capability to function described in the manner in the specification. In either case, the identifying information set forth in 37 C.F.R. ' 1.809(d) should be added to the specification if it is not already present. See 37 C.F.R. " 1.803-1.809 for additional explanation of these requirements.

Priority

Applicant's claim for domestic priority under 35 U.S.C. 120 is acknowledged. However, the applications upon which priority is claimed fails to provide adequate support under 35 U.S.C. 112 for claims 1, 2, 4, 5, 8, 9, and 11-15 of this application for the reasons provided above. See MPEP 706.02.

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (e) the invention was described in (1) an application for patent, published under section 122(b), by another filed in the United States before the invention by the applicant for patent or (2) a patent granted on an application for patent by another filed in the United States before the invention by the applicant for patent, except that an international application filed under the treaty defined in section 351(a) shall have the effects for purposes of this subsection of an application filed in the United States only if the international application designated the United States and was published under Article 21(2) of such treaty in the English language.
>
> (e) the invention was described in a patent granted on an application for patent by another filed in the United States before the invention thereof by the applicant for patent, or on an international application by another who has fulfilled the requirements of paragraphs (1), (2), and (4) of section 371(c) of this title before the invention thereof by the applicant for patent.

The changes made to 35 U.S.C. 102(e) by the American Inventors Protection Act of 1999 (AIPA) and the Intellectual Property and High Technology Technical Amendments Act of 2002 do not apply when the reference is a U.S. patent resulting directly or indirectly from an international application filed before November 29, 2000. Therefore, the prior art date of the reference is determined under 35 U.S.C. 102(e) prior to the amendment by the AIPA (pre-AIPA 35 U.S.C. 102(e)).

12. Claims 1, 2, 4, 5, 8, 9, and 11-15 are rejected under 35 U.S.C. 102(e) as being anticipated by Blaudin de The et al.(US 5,223,606).

Blaudin discloses nucleic acid encoding retinoic acid receptor (SEQ ID NO:2) which has approximately 82% amino acid sequence identity with the retinoic acid

receptor in Figure 1 of the present application. Blaudin discloses vectors and cells comprising the nucleic acid and the method of producing the protein with the transfected cell (columns 3-5).

13. No claims are allowed. The contiguous nucleic acid molecule disclosed in the figures 1B1-3 are free of the prior art.

14. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Michael Pak, whose telephone number is (571) 272-0879. The examiner can normally be reached on Monday through Friday from 8:30 AM to 2:00 PM.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Yvonne Eyler, can be reached on (571) 272-0871.

The fax phone number for the organization where this application or proceeding is assigned is (703) 872-9306.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is 703-308-1235.

Michael D. Pak

Michael Pak
Primary Patent Examiner
Art Unit 1646
29 December 2003